OPHTHALMIC MANIFESTATIONS OF HAEMATOLOGICAL MALIGNANCIES

DISSERTATION SUBMITTED FOR M.S. DEGREE (BRANCH III) OPHTHALMOLOGY MARCH 2009

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CERTIFICATE

This is to certify that this dissertation entitled "**OPHTHALMIC MANIFESTATIONS OF HAEMATOLOGICAL MALIGNANCIES"** is a record of the bonafide research work done by **Dr.M.SOUNDARAM** under my guidance and supervision in the Department of General surgery Madurai Medical College, Madurai under Dr.MGR. Medical University.

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DECLARATION

I, **Dr.M.SOUNDARAM**, Solemnly declare that the dissertation titled "**OPHTHALMIC MANIFESTATIONS OF HAEMATOLOGICAL MALIGNANCIES"** Has been prepared by me.

This is submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.S. (Ophthalmology) Branch – III degree Examination to be held in MARCH 2009.

Place : Madurai

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ACKNOWLEDGEMENT

I am deeply indebted to **Dr.P.THIYAGARAJAN, M.S., D.O.,** Professor and head of the department of ophthalmology, Madurai medical college, Madurai for the able guidance, inspiration and encouragement he rendered me at every stage of this study.

I express my heartful gratitude **to Dr.GITARAMANI M.S., D.O.,** and **Dr.UNNAMALAI M.S., D.O**.,, former head of the department of ophthalmology of madurai medical college, for their valuable advice and help in carrying out this study.

I acknowledge with gratitude the dynamic guidance and persistent encouragement given to me by my guide **Dr.T.BADRINARAYANAN, M.S., DO,** Assistant Professor in Ophthalmology, Department of Ophthalmology, Madurai Medical College, Madurai for having taken keen interest in sharing his ideas throughout the study period. His valuable suggestions and patronage has been a driving force to make this endeavor possible.

My sincere thanks to all the Assistant Professors for their valuable suggestions in carrying out this study.

I also thank my colleagues who extended their support at every step of this study.

I also thank **Dr.MUTHUKUMARASAMY M.D.D.M.,** Professor and Head of the Department of Medical Oncology, Madurai Medical College, Madurai for helping me with this study.

I also thank **Dr.S.M.SIVAKUMAR M.S.,** Dean in charge, Madurai Medical college, Madurai for permitting me to utilize the clinical materials of the hospitals.

I also thank **Dr. SIRISHKUMAR D.O., D.N.B.,** Head of the department of ophthalmology. Madurai Meenakshi Mission Hospital for allowing me to use their equipments for fundus photography.

Last, but not the least, my profound gratitude to all the ‘patients’, to whom I owe everything because, this venture would not have been possible with out them.

CONTENTS

INTRODUCTION

Knowledge of the intraocular manifestations of the leukemia's and lymphomas is important not only because of the frequency with which changes are seen but because the eye often reflects the disease state of the body. The ophthalmic symptoms may be the initial mode of presentation of the systemic illness. Indeed, prior to the use of bone marrow biopsy, the ophthalmologist was often called upon to assist with the diagnosis of the leukemia's.

Estimates of the frequency of intraocular involvement with leukemia range as high as 90% of cases. Although melanoma is the most common primary intraocular tumor in adults and retinoblastoma is the most common primary intraocular tumor in children, when secondary or metastatic neoplastic intraocular disease is considered, intraocular manifestations of hematological malignancies are found to be overwhelmingly more frequent.

Reticulum cell sarcoma is the lymphoma that most commonly involves the internal structures of the eye. The incidence of neoplastic intraocular involvement in patients with the lymphomas is probably much less than the incidence in patients with various leukemia's. The incidence of fundus abnormalities associated with anemia or thrombocytopenia probably parallels that seen in patients with the various leukemia's.

Almost all the structures in the orbit, adnexiae and eye can be involved in lymphoma. Lymphoma of the eye and adnexiae are most frequently of B lineage

Multiple myeloma is a plasma cell neoplasm which can exhibit a wide range of systemic and ocular signs and symptoms. Pars plana cysts are common and can be a striking ophthalmic finding. Uveal involvement has been reported by Bronstein.

Multiple myeloma is the most common of the plasma cell dyscrasias characterized by monoclonal gammopathy and osteolytic bone lesions. Ocular involvement in patients with multiple myeloma has been well described. The ocular manifestations may be divided into 2 groups: those attributable to myeloma infiltration in and about the eye, and the ocular consequences of hematologic and serum protein abnormalities. Infiltration of the iris has also been reported, simulating a nongranulomatous uveitis. A pseudohypopyon can also occur.

HISTORY

In the 1860s, Liebreich first described leukemic retinopathy. Since that time, virtually all intraocular structures have been found to become involved. 33 different ocular anomalies were listed by Goldbach from among the 242 leukemias at John Hopkins Hospital; of this majority are seen in the fundus.

Patients have been reported with leukemic infiltrates of the optic nerve, choroid, retina, iris, ciliary body, and anterior chamber.

In multiple myeloma, Bronstein reported plasma cells floating free in the anterior chamber and adhering to the posterior cornea.

A patient with polycythemia described by Lousea et al. had a one-and-a-half syndrome from an infarction of the pons.

In the study performed by Jabaily et al., visual disturbances occurred in 6 of 33 patients and included scintillating scotomas, episodic dimming of vision, and amaurosis fugax . Murphy et al. reported that 10 of 37 patients with essential thrombocythemia had visual phenomena as part of their disease. Among 33 patients reported by Michiels et al., 10 had visual symptoms: transient monocular blindness in 3, scintillating scotoma in 3, scintillations followed by transient monocular blindness in 1, and blurred vision in 10

PATHOPHYSIOLOGY OF HAEMATOLOGICAL MALIGNANCIES

The leukemia's are a invariably fatal systemic disease of unknown etiology, primarily involving the blood forming organs and characterized by widespread, rapid and disorderly proliferation of the leucocytes and their precursors, and by their presence at sometime during the disease of immature leucocytes in blood often in large numbers.

The leukemia's are often classified according to their type of cell that is preponderant in the peripheral blood or in marrow aspirations; they may be acute or chronic, and may affect the lymphatic, myeloid, monocytic and plasma cell elements. This reduces the field for practical purposes to the chronic myeloid and chronic lymphatic leukemia's (each representing a third of the incidence) while the remaining third consists of acute leukemia's (myeloid or lymphatic). In all types males are rather more commonly affected than females.

All types are characterized by moderately uniform enlargements of the lymph nodes (esp. the lymphatic group) and of the spleen (esp. the myeloid group). Chloroma is a form of acute myeloid leukemia of particular ophthalmologic interest since tumor like deposits of leukocytes, greenish in colour and locally invasive, form typically in the periosteum of the orbit, as well as long bones elsewhere in the viscera and in the lymph nodes. The green colour is due to choleglobin, derived from the

breakdown product of haemoglobin. Leukosarcoma is the analog of chloroma, occurring in ALL.

The pathologic alterations in all types of leukemia may be divided into two types: (a) those that are produced by the proliferation of leukemic cells within the blood-forming organs, particularly the bone marrow, spleen, and lymph nodes; and (b) those that are produced by infiltration of leukemic cells in other organs. Fatigue, pallor, and headache ensue. The bone marrow is invariably hyperplastic and reddish gray, whereas the degree of cellular proliferation in, with consequent enlargement of, the lymph nodes and spleen varies with the different types of leukemia. In organs that become infiltrated during the leukemic process, it is common to observe destruction of normal tissue and replacement by masses of leukemic cells. Organs most likely to be affected include the liver, lungs, kidneys, and gastrointestinal tract.

A variety of mechanisms are responsible for the clinical findings in patients with leukemia. A reduction in the normal number of blood-forming elements may result in anemia, which causes tissue hypoxia, ischemia, and infarction; leukopenia, which can result in increased susceptibility to infection; and thrombocytopenia, which can lead to spontaneous hemorrhage with infarction. Systemic, neurologic, and ocular dysfunction may occur from vascular thrombosis caused by the tumor cells themselves. Finally, tumor cells may invade the walls of

blood vessels, causing hemorrhage and allowing spread of the cells into the surrounding tissue.

Lymphoma's represent the most highly differentiated reticulo-endothelial hyperplasia which results in strictly localized aggregations of cells that most nearly resemble normal lymphoid tissue histologically. These benign swellings are commonest on the eyelids where they form ill-defined spongy tumors that may infiltrate back into the orbit or into the lacrimal gland. The symptoms are only due to mechanical embarrassment. Ptosis is thus the most common presenting sign, and proptosis and diplopia from limited movements, when within the orbit.

The cause of multiple myeloma is unknown. One theory is chronic antigenic stimulation of a plasma cell, which results in transformation and the development of myeloma. However, once a plasma cell is transformed, it is known to produce innumerable clones, which spread hematogenously to other myelogenous areas. Once there, these neoplastic cells form sheets that replace the normal bone marrow. In addition, the myeloma cells produce osteoclast-stimulating factor, a cytokine that results in bone destruction. The plasma cell activating factor interleukin-6 (IL-6) is found within bone marrow, resulting in plasma cell proliferation. The osteoblastic response in myeloma tends to be suppressed, resulting in the severe demineralization and bone destruction that are characteristic of the disease. Secondary hypercalcemia is present.

OCULAR CHANGES

The ocular changes are predominantly divided into anterior segment manifestations and posterior segment manifestations.

ANTERIOR SEGMENT MANIFETATIONS:

Sclera:

Infiltration of the sclera or episclera by leukemic cells is usually found at autopsy and rarely produces any clinical symptoms or signs. The cells are most often present in the episclera, with a perivascular distribution

Conjunctiva:

Involvement of the conjunctiva most often occurs in patients with lymphocytic leukemia, but it also occurs in other types. Cellular invasion occurs at all levels of the substantia propria. It may be diffuse or patchy, although it tends to concentrate around blood vessels. In some cases the involvement consists of visible nodules with surrounding injection resembling areas of focal episcleritis, whereas in others there is only slight swelling of the conjunctiva, and in still others there is diffuse and

substantial swelling leading to limitation of eye movements. As with other ocular manifestations of leukemia, conjunctival involvement may occur at any time during the course of the disease and may even be its first sign

The most frequent ocular findings were seen in conjunctiva (33.4%) among leukemics in a study in Poland (8). Multiple myeloma is one of the causes of a salmon patch conjunctival lesion.

Cornea:

Because the cornea is normally avascular, direct invasion by leukemic cells would not be expected. Leukemia can, however, induce formation of a sterile ring ulcer with iritis and pannus . This lesion, also called an immune ring, may occur before the diagnosis of leukemia is made; therefore, a patient with a corneal ring ulcer should be evaluated for leukemia as well as for other causes

Corneal precipitates have been reported as a complication of multiple myeloma for nearly 70 years. Corneal crystals have been identified as consisting of immunoglobulins, primarily IgG. Some data suggest that elevated immunoglobulin levels in tears or aqueous humor lead to corneal crystals, while other data suggest that the immunoglobulins reach the cornea through limbal vessels or that keratocytes supply the precipitated immunoglobulins(19). In one study, it

was seen that Confocal microscopy can enable the clinician to monitor the clinical response of multiple myeloma crystalline keratopathy to chemotherapeutic agents. It was found that numerous hyperreflective globules 6-11 nm in size were located within the corneal epithelium and anterior stroma. The development of the crystals can precede systemic evidence of multiple myeloma by several years. These crystals obscured normal architectural detail of the cornea in multiple myeloma. Lewis et al. reported the deposition of copper in both corneas at the level of Descemet's membrane in a patient with multiple myeloma and secondary hypercupremia. Copper was also deposited in the anterior and posterior capsule of the patient's lenses. Dry eye syndrome can occur as a manifestation of leukemia

Anterior chamber:

Anterior chamber leukemic cells and flare,pseudohypopyon and hyphema can occur in the anterior chamber. A shallow anterior chamber can be present due to iris swelling secondary to leukemic infiltrate.

Anterior chamber infiltration–simulating hypopyon (pseudohypopyon) can occur in multiple myeloma. A pseudohypopyon is characterized by its persistence and irregular contour, which suggest clumping of neoplastic cellular material rather than the layering of neutrophils, as in

anterior uveitis. Bronstein reported plasma cells floating free in the anterior chamber and adhering to the posterior cornea (10)

Uvea:

Cysts of the ciliary body represent the most common ocular manifestations in myeloma patients. Infiltration of the iris has also been reported, simulating a nongranulomatous uveitis. metastatic carcinomas of the iris, which typically appear as solid, amelanotic masses, occasionally are discohesive and shed cells that form a hypopyon in the anterior chamber (10)

Infiltration of the anterior segment by leukemic cells occurs rarely in patients. It usually occurs in patients with acute leukemia but may also occur in patients with chronic leukemia. In some patients, usually children, a spontaneous hypopyon-hyphema is the first evidence of the disease, whereas in other patients with known leukemia, involvement of the iris and anterior segment is the first or only evidence of relapse of the disease. The condition is characterized by conjunctival injection, symptoms of acute iridocyclitis, and a hypopyon that may be tinged with blood. There may be elevated intraocular pressure. Infiltration of the iris may be diffuse or nodular. Diffuse infiltration discolors the iris, which appears to be covered by a whitish-gray film, and it produces hyperchromia or hypochromia iridis when the process is unilateral. If

there is nodular infiltration, the nodules are seen over the iris. The diagnosis of anterior segment involvement by leukemia can be confirmed by paracentesis with cytologic examination of the aqueous humor. The condition can be treated effectively with low-dose irradiation to the anterior portion of the globe.

The choroid is commonly infiltrated by leukemic cells during the course of both acute and chronic leukemia. In fact, Leonardy et al. found the choroid to be the most frequently involved site (31.1%) of ocular involvement in an autopsy series of leukemic patients. Abnormalities that are visible during ophthalmoscopy, however, are rare. Nevertheless, some patients develop generalized serous detachment of the retina, retinal pigment epithelium, or both, associated with diffuse infiltration of the choroid by leukemic cells. Others develop localized choroidal masses with overlying retinal and RPE detachment, and rare patients develop pigmentary changes in the RPE from interference of the blood supply to the RPE by leukemic cells that infiltrate the choroid

Neuro-ophthal manifestations:

Third nerve palsy, lower facial nerve palsy and 6th nerve palsy have been reported.

CLL can present with acute optic neuropathy associated with cerebrospinal fluid evidence of meningeal spread of malignant cells (12).

Visual loss in myeloma is usually caused by compression or infiltration of the optic nerves by tumor (13).

The mechanism of optic neuropathy in this case is probably related to infiltration of the optic nerve meninges by malignant plasma cells and impaired vascular supply caused by aggregated intraluminal plasma cells and monoclonal hypergammaglobulinemia (14).

In one study, neuro-ophthalmic symptoms resulting in diplopia or visual disturbances were reported (21).

Neurological complications of leukemia are caused by a variety of different processes. First, neurologic injury may be caused by leukemic invasion of the leptomeninges, parenchyma, spinal cord, nerve roots, and peripheral nerves. Second, leukemia may cause cerebrovascular disorders, both hemorrhagic and ischemic, by obstructing intracranial vessels. Third, neurologic sequelae may result from the various forms of treatment of the disease. Fourth, some neurological disorders in patients with leukemia are paraneoplastic. In most cases, however, leukemic involvement of the CNS occurs from hematogenous spread or by direct invasion from adjacent affected bone marrow.

CNS leukemia is diagnosed by cerebrospinal fluid (CSF) analysis, requiring a minimum of five white blood cells per microliter and the presence of leukemic blast cells by cytospin technique.

Since the advent of successful therapy of leukemia, the meninges have become the major site of leukemic relapse. With the advent of intrathecal chemotherapy and cranial irradiation as routine CNS prophylaxis, the incidence of meningeal leukemia has declined to approximately 10%. For those who suffer meningeal involvement following radiation therapy, however, prognosis is poor. Meningeal involvement occurs more commonly in acute lymphoblastic leukemia than in acute myeloblastic leukemia and is rare in the chronic lymphocytic leukemias .

Meningeal leukemia occurs when the meninges are infiltrated by leukemic cells from the arachnoid veins. These cells then enter the CSF, including the Virchow-Robin spaces, penetrate the pia-glial membrane, and may invade brain parenchyma. On histopathology, the meninges show diffuse and focal invasion of leukemic cells, often in a perivascular configuration. Meningeal leukemia may produce a variety of symptoms from single as well as multiple cranial neuropathies and may also cause increased ICP. Affected patients may thus develop headache, meningismus, nausea, vomiting, papilledema, increasing lethargy, and focal neurologic signs, including diplopia from ocular motor nerve paresis. Papilledema occurs in up to 50% of such patients. The cranial sutures may be split in young children. Cranial neuropathies may result from infiltration of leukemic cells or from compression. Among the most

commonly involved are those with neuro-ophthalmologic impact, including the optic nerve, the oculomotor nerve, and the abducens nerve . Facial and vestibulocochlear neuropathies are also common, and the lower cranial nerves are occasionally affected.

In most cases, leptomeningeal and parenchymal infiltration occurs at a relatively late stage of the disease after the diagnosis is established, but this is not always the case. In a series of 30 children with neurological presentations of malignancy, one-third had acute leukemia. Papilledema and ocular motor neuropathies may be presenting manifestations of acute lymphocytic leukemia.

Leukemic involvement of the brain parenchyma is usually an extension of meningeal infiltration, but rare autopsy results document isolated leukemic parenchymal collections. These may be the result of a mechanism other than invasion from the meninges or from treatment that suppresses meningeal leukemic cells but spares those deep within the parenchyma. Parenchymal involvement is usually perivascular. More diffuse infiltration may be seen in hypothalamic presentations with symptoms of hyperphagia, obesity, and somnolence. Rarely, discrete tumor nodules are found. Rarer are chloromas, also called granulocytic sarcomas and myeloblastomas. These are collections of immature myeloid cells that are more common in the chronic form of the disease and that may also be seen in myeloproliferative disease. They may

precede the onset of leukemia, be a harbinger of transformation from chronic to acute forms, or signal a relapse. Chloromas are usually single, but they may be multiple. They may arise in various locations in the CNS parenchyma and dura. They are isointense to white matter on magnetic resonance (MR) T1- and T2-weighted images and are isointense to hypointense on computed tomographic (CT) imaging, enhancing with contrast.

Leptomeningeal infiltration can lead to infiltration of the intracranial portions of the optic nerves and optic chiasm. In most patients, visual loss may be slow and progressive, responding to radiation therapy, or extremely rapid. Cerebrovascular disorders may produce neurological dysfunction in patients with leukemia. The majority is hemorrhagic, caused by invasion of blood vessel walls by leukemic cells, thrombocytopenia, sepsis, and disseminated coagulopathy. Blast crisis, extreme leukocytosis, and thrombocytopenia are predisposing factors. Intracranial hemorrhage contributes to mortality in 10 to 21% of leukemic patients. Cerebral ischemia is less common than hemorrhage and may result from arterial or venous obstruction. In leukemic patients, cerebral venous thrombosis is the most common form of infarction, resulting in focal neurologic deficits, increased ICP, and papilledema. Arterial infarction may involve large vessels, cause lacunar events, or result from septic emboli.

Patients with leukemia may develop neurological dysfunction from the toxic effects of drugs used to treat the leukemia and from infections that occur in the CNS of patients who are debilitated or immunosuppressed. With conventional cranial radiotherapy, neurotoxicity is more often subacute and delayed, rather than acute. Intrathecal methotrexate may cause chemical meningitis. A subacute leukoencephalopathy occurs in patients treated with methotrexate and is thought to be caused by direct toxicity of the drug. It is more commonly encountered when methotrexate is given in high doses intravenously and intrathecally and/or combined with cranial irradiation, and it occurs in up to 50% of children undergoing such therapy. Other drugs may produce a similar encephalopathy, a peripheral neuropathy, or both.

Neurological disturbances in patients with Hodgkin's disease may result from involvement of the intracranial portion of the CNS, the spinal cord, or the peripheral nervous system (PNS). According to some authors, involvement of the nervous system in patients with Hodgkin's disease occurs in 13 to 15% of all cases , although a review of 2,185 patients with Hodgkin's disease found only 12 (0.5%) who developed neurological symptoms, signs, or both . This discrepancy may be related to increasingly early diagnosis and treatment of this condition. Most examples of neurological involvement are secondary, occurring from

discrete or diffuse metastases via meningeal vessels or from direct tumor extension.

When involvement of the meninges is primarily intracranial, single or multiple cranial neuropathies with and without papilledema commonly occur. In addition, single or multiple tumor nodules may implant on the meninges and enlarge, ultimately compressing and invading the substance of the brain and producing focal neurological defects.

Single or multiple intracranial masses may develop in patients with systemic Hodgkin's disease. These lesions may be located anywhere within the cranial vault. In such cases, the symptoms and signs are related to the location and size of the lesion. They include focal or generalized seizures, focal neurological signs, confusion, mental deterioration, and coma. Visual disturbances in such cases include visual hallucinations, unilateral or bilateral visual loss from invasion of the optic nerves, visual field defects indicating chiasmal dysfunction, or homonymous hemianopic field defects from damage to the postchiasmal visual sensory pathway. A cavernous sinus syndrome with multiple cranial nerve pareses may occur, but diplopia and ptosis may also result from invasion of the brainstem and disruption of the cranial nerve nuclei or their fascicles.

Peripheral neuropathy affects some patients with Hodgkin's disease. Patients with Hodgkin’s disease can also have Horner syndrome from damage to the oculosympathetic pathway or paralysis of the diaphragm

from damage to the phrenic nerve. As is the case with CNS dysfunction, involvement of the PNS is usually a secondary phenomenon in patients in whom systemic Hodgkin's disease has previously been diagnosed.

Evidence of central (and occasionally peripheral) nervous system dysfunction in patients with Hodgkin's disease generally appears late in the course of the disease. Nevertheless, such dysfunction may occur as the initial and only manifestation of the process, months or years before any other evidence of Hodgkin's disease appears.

In some instances, a patient has constitutional symptoms or laboratory evidence compatible with Hodgkin's disease, but the diagnosis is not suspected until the CNS lesion is biopsied or, if that lesion is incorrectly diagnosed, not until months or even years later. This is particularly true when visual loss is the primary disturbance. In addition to visual loss from damage to parts of the visual sensory pathway and diplopia from damage to the ocular motor nuclei, fascicles, and nerves, Hodgkin's disease may produce visual symptoms from involvement of ocular structures, although this is uncommon. Ocular abnormalities associated with Hodgkin's disease include uveitis and retinopathy, keratitis sicca with bilateral enlargement of the parotid glands, and keratitis with vascularization. Siatkowski et al. reported a 21-year-old man who developed a left optic neuropathy associated with ipsilateral orbital pain after being in clinical remission of Hodgkin's disease for 2

years. The left optic disc showed moderate swelling with a few peripapillary hemorrhages. MR imaging showed diffuse enhancement of the nerve following intravenous administration of gadolinum-DTPA. The CSF was under normal pressure, had a normal concentration of protein and glucose, and contained no cells on standard or cytopathologic examination. Because of the suspicion of lymphomatous infiltration of the optic nerve, the patient was treated with 2000 cGy radiation, intravenous methylprednisolone, and oral prednisone. Over the next 6 weeks, vision improved, and the disc swelling resolved. Biopsy of a cervical lymph node revealed evidence of recurrent Hodgkin's disease.

Patients with Hodgkin's disease (and patients with other lymphomas) may develop neurologic dysfunction, visual dysfunction, or both from paraneoplastic disorders. These disorders, which include encephalitis, encephalomyelitis, cerebellar degeneration, peripheral sensory and motor neuropathies, acute and chronic dysautonomia, cancer-associated retinopathy, and optic neuropathy, occur in a wide variety of malignancies and are thought to be caused by immune-mediated remote effects of the cancer. Kay et al. Reported a patient who developed opsoclonus-myoclonus syndrome after treatment of Hodgkin's disease by chemotherapy and autologous bone marrow transplantation. These authors speculated that chemotherapy resulted in breakdown of lymphomatous tissue and the production of antineuronal antibodies. A

patient described by Abrey developed myasthenia gravis characterized by ptosis, diplopia, generalized weakness, and dysphagia in the setting of extrathymic Hodgkin's disease. When the Hodgkin's disease was treated with antineoplastic therapy, the myasthenia gravis completely resolved, suggesting a paraneoplastic etiology.

Neurological dysfunction in patients with multiple myeloma may be caused by compression of neural tissue by single or multiple tumors or by displaced bone; meningeal dissemination with infiltration of neural tissue by tumor cells; systemic complications of the disease (e.g., metabolic or hematologic disturbances, infection); and complications of therapy for multiple myeloma rather than from the disease itself.

The neural structure most susceptible to compression is the spinal cord. Compression of the spinal cord may occur from an extradural plasmacytoma that originates within one or more of the vertebral bodies or in the epidural space. Compression may also occur from the effects of a plasmacytoma within the subdural or subarachnoid space. Neural structures other than the spinal cord may be compressed by myeloma cells or adjacent, diseased bone. These structures include the spinal nerve roots, the cranial nerves, and the brain parenchyma.

When spinal nerve roots are compressed, patients develop a radiculopathy that may be characterized by motor signs, sensory changes, and abolition of deep-tendon reflexes. Not all cases of polyneuropathy are

associated with evidence of nerve root compression, however. Some appear to be paraneoplastic, i.e., related to a secondary or distant effect of the myeloma.

Cranial neuropathy occurs less frequently in patients with multiple myeloma than does spinal cord or nerve root compression. Nevertheless, almost any cranial nerve may be affected, either in isolation or in combination with other cranial nerves. In some cases, there is associated lethargy and a generalized decrease in the level of consciousness from diffuse meningeal involvement by myeloma cells.

Intracranial plasmacytomas, either in the setting of multiple myeloma or as isolated lesions in patients with no systemic evidence of multiple myeloma, may produce a variety of focal neurologic signs from compression of adjacent brain tissue, or they may cause increased ICP from a generalized mass effect or from obstruction of the dural venous sinuses. In most cases, the brain is involved by extension of the tumor from the calvarium, the dura overlying the cerebral and cerebellar hemispheres, or the falx cerebri; however, in rare instances, there are solitary or multiple plasmacytomas that have no osseous or dural component. It is in such cases that systemic evidence of multiple myeloma is least likely to be found, and treatment is usually directed toward surgical removal of the lesions followed by radiation therapy. Multiple myeloma may infiltrate neural tissue as well as compress it. This

is particularly true with regard to cranial neuropathies; however, infiltration without evidence of a mass lesion may also occur in brain parenchyma.

Patients with multiple myeloma develop a peripheral neuropathy which may be sensory, motor, or mixed sensorimotor type. When it is purely sensory, patients complain of numbness, pain, or both; when it is purely motor, it is characterized by slowly progressive, painless weakness of the extremities. Patients with the mixed sensorimotor type of peripheral neuropathy experience slowly progressive distal numbness, hypesthesia, and weakness, usually affecting the legs more than the arms. Nerve conduction studies are abnormal in all cases, regardless of the type of peripheral neuropathy. In some cases, the peripheral neuropathy is related to systemic amyloidosis or a sclerotic form of multiple myeloma; however, in most cases there is no evidence of either compression or infiltration of the involved neural tissue nor is there any evidence that the process is related to the metabolic or hematological effects of the disease. It may be present before the diagnosis of multiple myeloma, and its course is usually independent of the course of the myeloma. The neuropathy thus bears close resemblance to the carcinomatous neuropathies that occur as paraneoplastic phenomena associated with certain types of systemic malignancies and are thought to be autoimmune in origin. Indeed, in about 40% of patients with peripheral neuropathy

associated with multiple myeloma or one of the other monoclonal gammopathies, IgM reacts with myelin or with the intermediate filament vimentin that is found in high concentrations in Schwann cells. Finally, the therapy of multiple myeloma may also produce neurological dysfunction.

Because of its proximity to the base of the skull and its long extradural course, the abducens nerve is the cranial nerve most commonly affected by multiple myeloma, and it is also commonly involved by plasmacytomas located at the base of the skull. The dysfunction may be unilateral or bilateral. It may be isolated, or it may occur in association with other cranial neuropathies, including optic neuropathy. Cranial nerves other than the abducens nerve, including the vestibulocochlear and trigeminal nerves and the other ocular motor nerves, can be damaged by multiple myeloma and plasmacytomas. As with abducens nerve paresis, paresis of the oculomotor or trochlear nerves that occurs in these settings can be isolated or associated with other neurological abnormalities. The paresis may be the first sign of the disease, or it may occur late in the course of the disease. Rare cases of ocular motor nerve paresis are bilateral, thus mimicking an intrinsic brainstem process, but most are unilateral.

Orbit:

Orbital infiltrarions are reported in leukemia. Orbital plasmacytoma can be the first manifestation in certain cases of multiple myeloma (20).

All types of leukemia may involve the orbit; however, such involvement occurs more frequently in acute leukemia than in chronic leukemia. Leukemia is therefore a not infrequent cause of proptosis in children. Various authors report that 2 to 11% of children with proptosis have some form of acute leukemia. The orbital involvement may be related to infiltration of soft tissue by leukemic cells, to hemorrhage, or to both.

Orbital infiltration in leukemia causes proptosis, diplopia, edema of the eyelids, chemosis of the conjunctiva, and moderate to severe pain, thus mimicking an orbital cellulitis. It usually occurs in patients with previously diagnosed leukemia, but in some cases, it is the first evidence of the disease.

Leukemic cells may infiltrate almost all of the structures in the orbit, including the extraocular muscles, fat, and lacrimal gland. Leukemic infiltration may even extend beyond the confines of the orbit into the paranasal sinuses. It is usually diffuse, but in some patients, the infiltration produces a relatively well-circumscribed mass of leukemic cells. Although such a mass can accompany any form of leukemia and

can be observed in patients with chronic leukemia after long periods of remission, it occurs most often in patients with acute myelogenous leukemia. In such patients, the mass may have a characteristic greenish appearance caused by the pigmented enzyme myeloperoxidase and is called, as noted above, a granulocytic sarcoma or chloroma. The cause of granulocytic sarcoma is unknown, but cellular immune deficiency may play an important role. Granulocytic sarcomas may appear at any time during the course of the leukemia and, like diffuse infiltration, may even occur months or even years before there is any evidence of other systemic disease. In patients with leukemia, bilateral involvement of the orbits is not uncommon. It is usually a poor prognostic sign

Granulocytic sarcoma or chloroma is an unusual localized tumor composed of cells of myeloid origin. Involvement of the orbit and the ethmoid sinuses and presenting as proptosis is rare (22).

Orbital involvement is a rare complication of Hodgkin's disease. The majority of cases occurs in patients with known Hodgkin’s disease and consists of infiltration of the eyelids, subconjunctival space, conjunctiva, soft tissues of the orbit, and lacrimal gland. In some Patients with multiple myeloma may develop signs of an orbital process as the result of their myeloma. Such patients may present with proptosis, diplopia, visual loss, or a combination of these manifestations. Eye, brow, or orbit pain may be a prominent complaint, although this is by no means

always the case. Some of these patients have multiple myeloma at the time their orbital symptoms and signs develop, but in most, the orbital process is the first sign of the disorder. In these patients, myeloma cells usually infiltrate orbital soft tissue. The infiltration is often diffuse, affecting all of the tissues in the orbit, including fat, extraocular muscles, and lacrimal gland, but it also may be limited, presenting as focal enlargement of the lacrimal gland or as a well-defined mass. Orbital involvement is usually unilateral, but it may be bilateral. In rare cases, the orbital disease is not caused by infiltration by myeloma cells per se but by amyloidosis, which may occur in patients with multiple myeloma and is usually homologous with portions of the immunoglobulin light chains that are produced in abundance as a consequence of the disease.

As is the case with intracranial disease, some patients have a solitary plasmacytoma within the orbit unassociated with any systemic evidence of multiple myeloma. It is important to remember, however, that although such patients may have no evidence of systemic multiple myeloma at the time that the orbital lesion becomes apparent, only long-term observation can truly establish if the lesion is a benign, localized collection of

Plasma cells or an early manifestation of systemic multiple myeloma. Involvement of the orbit is the first sign of the disease in a few cases.

Opportunistic infections:

Bilateral herpes simplex dendritic corneal ulcer and herpes zoster vesicles can occur. *Pseudomonas* panophthalmitis causing scleral and corneal melt. *Branhamella catarrhalis* corneal ulcer can progress to phthisis bulbi can also occur (9).

Bilateral endogenous *Fusarium* endophthalmitis as the initial manifestation of a disseminated infection in a patient with hematological malignancy (18)

Patients with AIDS are at higher risk for developing Hodgkin's lymphoma. As in patients without AIDS, the disorder may present with a variety of manifestations. In patients with AIDS, orbital and sinus involvement can be the initial presentation of Hodgkin's disease.

The neurological and visual dysfunctions that occur in patients with Hodgkin's disease are not always related to the direct effects of the disease. Some patients with Hodgkin's disease develop infections or inflammations related to their debilitated and often immunosuppressed state. These include cryptococcal meningitis, aspergillosis, cytomegalic inclusion disease, herpes zoster, PML, and granulomatous angiitis of the CNS.

POSTERIOR SEGMENT MANIFESTATIONS

The posterior segment manifestations of haematological malignancies can be divided into1) direct manifestations (leukemic infiltrates), 2) possible direct manifestations (such as white-centered retinal hemorrhages), 3) manifestations of complications of malignancy (chiefly anemia, thrombocytopenia, and hyperviscosity states) and 4) opportunistic infections. Finally, there may be5) chance or unrelated findings.

Multiple myeloma is a neoplasm of plasma cells producing an excess of one type of immunoglobulin. The main ocular features are those araising from the local orbital/intracranial presence of the osteolytic lesions or from the effect of increased viscosity with retinal haemorrhages / vascular occlusion.

Retinal or preretinal infiltrates:

Leukemic infiltrates have been described by Kuwabara. A patient with chronic myelogenous leukemia with large gray-white nodules of varying sizes in the retina was reported. Gray-white streaks along vessels may be caused by perivascular leukemic infiltrates. Infiltrates are also observed in the retina in systemic lymphomas also.

Choroidal infiltrates:

Although the choroid is probably the most commonly affected part of the eye in leukemia's, clinical signs of choroidal involvement are often subtle unless there is overlying retinal changes which bring them to attention. Serous retinal detachment overlying choroidal infiltrates or overlying frank choroidal masses are important clues. Serous retinal detachment overlying areas of choroidal infiltration have been reported in patients with CLL, ALL, CML and AML. Serous retinal pigment epithelial (RPE) detachment has also been reported in a patient with acute lymphoblastic leukemia. The serous retinal and RPE detachments can be the presenting manifestation of the leukemia. Eventually, as the changes resolve, coarse clumping of the RPE is seen. Areas of RPE hyperplasia including heaped-up masses of pigment epithelium surrounding leukemic cells.

The choroid is commonly infiltrated by leukemic cells during the course of both acute and chronic leukemia. In fact, Leonardy et al. found the choroid to be the most frequently involved site (31.1%) of ocular involvement in an autopsy series of leukemic patients. Abnormalities that are visible during ophthalmoscopy, however, are rare. Nevertheless, some patients develop generalized serous detachment of the retina, retinal pigment epithelium, or both, associated with diffuse infiltration of the choroid by leukemic cells. Others develop localized choroidal masses

with overlying retinal and RPE detachment, and rare patients develop pigmentary changes in the RPE from interference of the blood supply to the RPE by leukemic cells that infiltrate the choroids

Vitreous infiltrates:

Vitreous opacities may be manifestations of an intraocular malignancy. Moribund patients may show massive collections of tumor cells in the vitreous, but most patients with intravitreal hemorrhage have neoplastic cells in the vitreous only because their peripheral blood contains tumor cells. The cells do not appear to be preferentially replicating in the vitreous cavity.

Leukemic cells have been found in the vitreous of patients with neovascularization of the disc. Disc neovascularization has also been seen in a patient with erythroleukemia although that patient also had diabetes. Vitreous involvement has been seen at the time of autopsy in patients with reticulum cell sarcoma, Burkitt's lymphoma, multiple myeloma, and Hodgkin's disease

In leukemia the internal limiting membrane usually acts as a barrier to infiltration of the vitreous by leukemic cells; however, such infiltration occasionally occurs. Terson syndrome occurs in rare cases.

White-centered retinal hemorrhages (Roth spots):

Most patients are asymptomatic or have visual loss related to the underlying disease process. White-centered retinal hemorrhages may be isolated or more numerous,

Depending on the association. White-centered hemorrhages most likely result from

Localized capillary rupture from any anoxic insult or sudden elevation in venous pressure. The white center is a fibrin platelet aggregate that results during the physiologic

Healing process. The collections of abnormal white blood cells (leukemia/lymphoma) or platelets (multiple myeloma). The most common underlying factors are anemia and thrombocytopenia.

Manifestations of anemia and thrombocytopenia:

Leukemic retinopathy is the term most often used to denote the fundus manifestations of anemia, thrombocytopenia, and increased blood viscosity seen in patients with leukemia. In general, the term does not necessarily refer to frank leukemic proliferation. The changes of "leukemic retinopathy" may be more commonly seen with the acute leukemias but the frequency with which they occur has not been adequately studied to be certain. Although perivascular sheathing may be

due to actual perivascular infiltrates, tortuous dilation of the retinal veins probably is not. The veins and arteries may assume a yellowish tinge both because of anemia and leukocytosis. Retinal hemorrhages may be seen, often at the posterior pole. The hemorrhages may be subretinal, deep retinal, superficial retinal, or preretinal, and there may be breakthrough bleeding into the vitreous cavity. They may have a blot or blotch shape, flame shape, or they may have white centers.

Cotton-wool spots may be the presenting abnormality that precipitates the systemic evaluation leading to the diagnosis of leukemia. The cotton-wool spots may be due to local factors, such as an abnormally large cell or cluster of cells occluding retinal arterioles, and may not be related to the overall peripheral blood composition. In general, hematologic parameters are not associated with the presence of cotton-wool spots. Cotton-wool spots and hemorrhages can resolve in patients with chronic disease.

Retinal hemorrhages and cotton-wool spots related to anemia or thrombocytopenia are common in patients with non-Hodgkin's lymphoma, but direct retinal involvement of the retina in patients with systemic lymphoma is extremely rare. Hodgkin’s disease can cause periphlebitis, focal chorioretinitis, vitreitis, and optic disc edema Patients with "numerous white deposits in the retinal periphery," chorioretinitis, Roth's spots, and perivascular retinitis have been reported

In multiple myeloma the most common retinal findings include manifestations of anemia and thrombocytopenia such as flame-shaped or white-centered hemorrhages and nerve fiber layer infarcts.

Manifestations of hyperviscosity:

Whole-blood hyperviscosity may lead to veno-occlusive disease, microaneurysm formation, retinal hemorrhages, and retinal neovascularization. The most common manifestation is probably a mild or "hyperpermeable" central retinal vein occlusion. A systemic hyperviscosity state should be suspected in patients with bilateral changes. Peripheral retinal neovascularization has been reported in patients with CML in association with peripheral capillary nonperfusion. Most cases have associated extreme leukocytosis or thrombocytosis. Presumably, the hyperviscosity state leads to peripheral nonperfusion and subsequent development of retinal neovascularization.In general, the blood viscosity begins to increase remarkably only with white blood cell counts of greater than 50,000.

In multiple myeloma Increased viscosity results in reduced flow of blood through the eyes and produces the characteristic changes of dilataion of the retinal arteries and veins, hemorrhages, microaneurysms and areas of capillary closure.

Microaneurysm formation may be apparent, most frequently in the retinal periphery and mid periphery. If hyperviscosity is severe, retinal changes similar to those described in Waldenström's macroglobulinemia may be seen. Serous and exudative retinal detachments associated with multiple myeloma have also been reported. Reduction in the abnormalities producing hyperviscositoes can reverse retinal changes.

Optic Neuropathy:

Visual loss in myeloma is usually caused by compression or infiltration of the optic nerves by tumor. Bilateral optic disc swelling can be the initial clinical manifestation of multiple myeloma. The mechanism of optic neuropathy is probably related to infiltration of the optic nerve meninges by malignant plasma cells and impaired vascular supply caused by aggregated intraluminal plasma cells and monoclonal hypergammaglobulinemia.

Optic nerve head infiltration with acute lymphoblastic leukemia has also been described

In the past, leukemic infiltration of the orbital portion of the optic nerve (like that of the intracranial portion) occurred in the late stages of the disease, usually as a preterminal phenomenon. Since the advent of sophisticated chemotherapeutic regimens and the use of prophylactic CNS irradiation in the treatment of leukemia, the prognosis for long-term

survival has improved so dramatically that leukemic invasion of the optic nerve is not uncommon and should be considered a treatable cause of vision loss. Clinical evidence of infiltration of the orbital portion of the optic nerve occurs primarily in children and adults with acute leukemia, especially those with the acute lymphocytic variety. Histopathologically, however, optic nerves from patients with acute leukemia are only slightly more likely to show evidence of leukemic infiltration than are nerves from patients with chronic leukemia. Although active bone marrow disease as well as involvement of the CNS is usually present at the time the infiltration becomes evident, optic nerve infiltration may be the first manifestation of recurrence leukemia or relapse.

Leukemic infiltration of the optic nerve may produce two distinct clinical patterns. In one pattern, the prelaminar and laminar portions of the optic nerve are infiltrated; in the second pattern, the infiltration is retro laminar. Infiltration of the optic disc occurs less frequently than does retrolaminar infiltration.

When the optic disc is infiltrated, the appearance is that of a fluffy, whitish infiltrate within the substance of the disc. The infiltrate is usually associated with disc swelling and hemorrhage. In this setting, the visual acuity is usually normal or only minimally reduced, although if the infiltration, swelling, or hemorrhage extend into the macula, significant impairment of central vision may occur.

Leukemic infiltration of the retrolaminar portion of the optic nerve is associated with a variable degree of optic disc swelling. The fluffy appearance that is characteristic of optic disc invasion is absent in such cases, but an associated retinopathy that includes evidence of both arterial and venous occlusion may be present. Although leukemic infiltration of the retrolaminar portion of the optic nerve may be compatible with normal visual function, there is usually moderate to severe loss of vision.

Because both patterns of leukemic infiltration of the optic nerve are associated with some degree of optic disc swelling, they must be differentiated from papilledema. In many cases, this is extremely difficult, not only because in all three settings there is optic disc swelling associated with minimal if any visual loss, but also because it is not unusual for optic nerve infiltration to occur simultaneously with meningeal infiltration and increased ICP , particularly in the setting of treatment of acute promyelocytic leukemia with all-trans retinoic acid . For this reason, in all patients who present with optic disc swelling in the setting of leukemia, neuroimaging studies and a lumbar puncture must be performed. Both CT scanning and MR imaging typically show generalized enlargement of the affected optic nerve often associated with a cuff of enhancement surrounding the nerve that represents leukemic cells. Ocular echography may also be helpful in this setting, showing that the nerve itself is enlarged.

The treatment of leukemia is discussed below; however, it is appropriate here to emphasize that the optimum treatment for infiltration of the optic nerve is prompt local irradiation. This is typically performed urgently and followed by intrathecal as well as systemic chemotherapy. Patients who receive about 2000 cGy to the posterior globe and orbit usually show a rapid resolution of their disc swelling and infiltration that may be accompanied by improvement in vision.

In addition to infiltration, neovascularization of the optic disc occurs in patients with acute leukemia, particularly the lymphocytic type An optic chiasmal syndrome may be produced by a plasmacytoma that mimics a pituitary adenoma. Homonymous field defects in patients with multiple myeloma may result from compression or infiltration of the postchiasmal visual sensory pathways by myeloma cells, from secondary effects of the disease (e.g., infarction of the occipital lobe), or from infectious complications of the disease, its therapy, or both (e.g., intracranial abscess formation

Vascular Occlusions:

Visual disturbances in patients with essential thrombocythemia are related to thrombotic, hemorrhagic, and possibly vasomotor phenomena. For example, patients may experience embolic retinal artery occlusions, amaurosis fugax, or CRVO.

The ocular abnormalities seen in patients with polycythemia vera are similar to those seen in patients with other hyperviscosity syndromes. Their severity is related to that of the polycythemia and its duration. Many patients develop engorgement of the conjunctival and retinal vessels. The associated ischemic disorders of the eye may become manifest as dilated, tortuous vessels, retinal hemorrhages, central retinal artery occlusion (CRAO), central retinal vein occlusion (CRVO), and anterior ischemic optic neuropathy (AION). CRVO may be bilateral. As mentioned above, papilledema may result from the effects of thrombosis of the cerebral venous sinuses. Optic disc swelling may also result from local vascular changes related to hyperviscosity

Patients with multiple myeloma often have retinal vascular abnormalities that appear to be related not to infiltration of the eye by myeloma cells but to the hyperviscosity that accompanies the systemic disease. The increased viscosity leads to reduction in blood flow in the retina and secondary ischemia. In the early stage of the disease, the main changes are in the veins, which become dilated and somewhat tortuous. As the process progresses, these vessels show segmentation with sausage-like dilations and constrictions. Progression produces intraretinal hemorrhage, exudation, and microinfarcts (cotton-wool spots). Eventually, the patient may suffer a branch retinal vein occlusion or a CRVO that may be unilateral or bilateral. Rarely, retinal findings presage

the diagnosis of multiple myeloma. Histopathologic studies of patients with retinopathy in the setting of multiple myeloma demonstrate a variety of abnormalities, including dilation and occlusion of retinal veins, retinal hemorrhages, exudates, microaneurysms, microthrombi in small retinal vessels, serous detachment of the neurosensory retina, and detachment of the RPE. These changes are not specific for multiple myeloma; however, they also occur in patients with hyperviscosity syndromes from other causes

Opportunistic infections:

Opportunistic infections are common in immunosuppressed patients. Cytomegalovirus (CMV) is one of the most common causes of infectious retinitis in patients with altered immune status. The various herpesviruses can cause infectious retinitis as well. An unusual case of mumps uveitis in a patient with acute lymphocytic leukemia has been reported. Among parasitic infections, ocular toxoplasmosis is the most common. Fungal intraocular involvement is a frequent and severe problem.

A patient with Hodgkin's disease with widespread severe destruction of the sensory retina was due to disseminated herpes zoster infection and viral retinitis of this type is known to occur in immunocompromised hosts.

Opportunistic infections are common in patients with Hodgkin's lymphoma. Toxoplasmic uveitis and chorioretinitis, Nocardia infection, and virtually all viral infections of the herpes family are known to occur.

AIM OF THE STUDY

- To study the incidence of ophthalmologic manifestations in hematological malignancies
- To study the types of clinical manifestations in hematological malignancies

MATERIALS AND METHODS

- The study was conducted at Government Rajaji Hospital, madurai for a period of 18 months from February ’07 to August ‘08
- The following patients were selected for this study:
- ✓ Patients with haematogenous malignancies including
- ✓ Leukemia’s- Acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia
- ✓ Multiple myeloma
- The patients who were refered to ophthalmology op with haematological malignancies for ophthal evaluation.
- Those patients with haematologic malignancies registered in the oncology department.
- Paediatric patients with haematologic malignancies
- The patients were graded according to
- ✓ Age
- ✓ Sex
- ✓ Duration after diagnosis of malignancy
- ✓ Type of ophthalmic manifestation
- ✓ Visual acuity at the time of presentation

- All patients were subjected to detailed ophthalmologic examination including visual acuity, external ocular examination, slit lamp examination and schiotz tonometry. The pupil was dilated with 1% tropicamide eye drops and detailed fundus examination with both direct and indirect ophthalmoscopy was done. Fundus photography was done for selected cases. Blood smear investigations were done for all the patients to diagnose the type of hematological malignancy. Bone marrow examination was also done for selected patients.
- Those patients with haematological non-malignant condition were excluded from this study.

OBSERVATION

Out of the fifty patients with hematological malignancy, 22 patients were found to have ocular features.

AGE INCIDENCE:

In this study, age of the patient's with hematological malignancy varied from 2 yrs to 72 yrs, and the ocular features also presented in a wide range of age group.

Age (in yrs)	No: of patients	Ocular features
0-9	6	6
10-19	8	3
20-29	9	5
30-39	10	2
40-49	10	3
50-59	4	0
60-69	2	2
70-79	1	1

Among those patients with ocular features, the posterior segment findings were predominant among all age groups than the anterior segment involvement.

Age (in yrs)	Ocular features	Anterior Segment	Posterior Segment
0-9	6	1	5
10-19	3	1	2
20-29	5	2	3
30-39	2	1	1
40-49	3	2	3
50-59	0	0	0
60-69	2	1	1
70-79	1	0	1

SEX INCIDENCE:

There were totally fifty patients included in this study. Out of the fifty patients included in this study, 32 were males and18 were females. Out of the 32 males, 16 had ocular findings, and 7 out of 18 females had ocular features.

	Males	**Females**
Total cases	**32**	**18**
Ocular features	**16**	**7**
Anterior segment features	**2**	**1**
Posterior segment features	**12**	**4**
Neurological findings	**3**	**2**

Among the ocular features, anterior segment findings were present in 2 males and 1 female. Neurological involvement was in 3 males and 2 females. Posterior segment findings were present in 11 males and 4 females, showing that posterior segment involvement were more common than anterior segment or neurological involvement.

INCIDENCE OF OCULAR FEATURES AMONG INDIVIDUAL DISEASES:

Among all the individual hematological malignancies, Chronic Myeloid Leukemia presented with maximum of 75% incidence of ocular features, followed in equal frequency of both ALL and AML, about 66.6% each. The least in the order was Hodgkin's disease of 11.1%. In between were multiple myeloma of 45.4%,Non-Hodgkin's disease 28.5% and CLL 25%.

Type of disease	Total cases	Ocular features	Percentage
HD	**9**	**2**	**22.2**
CLL	**4**	**1**	**25**
NHL	**7**	**2**	**28.5**
MM	**11**	**5**	**45.4**
AML	**6**	**4**	**66.6**
ALL	**9**	**6**	**66.6**
CML	**4**	**3**	**75**

The incidence of Posterior segment findings were more in each of the individual diseases over the anterior segment findings, except AML

which had an equal incidence and CML were in there were 2 cases with anterior segment findings and only one with posterior segment findings.

Type of disease	Ocular features	Anterior Segment	Posterior Segment
NHL	**2**	**0**	**2**
HD	**2**	**1**	**2**
MM	**5**	**2**	**3**
CML	**3**	**2**	**1**
CLL	**1**	**0**	**1**
AML	**4**	**2**	**2**
ALL	**6**	**1**	**5**

DIFFERENT TYPES OF OCULAR MANIFESTATIONS:

Among the different types of ocular manifestations, posterior segment findings had a greater incidence with equal dominance of retinal and pre-retinal hemorrhages of 4 cases each. Followed next in frequency was Roth spots and nerve palsies including 3rd and 6th nerve palsies with ptosis and diplopia of 3 cases each. Next in order was vitreous hemorrhage and posterior uveitis with 2 cases each. All the rest of the features like proptosis, sub-retinal haemorrhages, anterior uveitis,

papilledema, sclerokeratitis, retinal detachment and dry eye were present in 1 case each.

Ocular manifestation	No: of cases	Percentage
RH	**4**	**16**
PRH	**4**	**16**
RS	**3**	**12**
NP	**4**	**16**
VH	**2**	**8**
PU	**2**	**8**
Proptosis	**2**	**8**
AU	**1**	**4**
SRH	**1**	**4**
Papilledema	**1**	**4**
RD	**2**	**8**
Scerokeratitis	**1**	**4**
Dry eye	**1**	**4**

VISUAL ACUITY AT THE TIME OF PRESENTATION:

About 42 eyes of 26 patients had a fairly good visual acuity of about 6/6 – 6/9. 22 eyes of 17 patients had a visual acuity of 6/12 – 6/18 and 21 eyes of 15 patients 6/24 – 6/36 respectively. Remaining 15 eyes of 11 patients had an acuity ranging from 6/60 to PL+. T One patient with Hodgkins lymphoma who presented with RE-axial proptosis with cavernous sinus infiltration with total retinal detachment had no perception of light.

There was a 21/2 yrs old male child who presented with axial proptosis of his right eye, had a poor visual acuity of perception of light. Another 2 yrs old male child with RE-vitreous haemorrhage and LE-RD with subretinal hemorrhage had an acuity of CFCF in his RE and HM in his LE.

Visual Acuity	**No: of eyes**	**Percentage**
6/6-6/9	**42**	**42**
6/12- 6/18	**22**	**22**
6/24- 6/36	**21**	**21**
6/60 or <	**15**	**15**

DISCUSSION

With evolving diagnostic and therapeutic advances, the survival of patients with hematological malignancies has considerably improved. This has led to an increase in the variability of ocular presentations in the form of side effects of the treatment and the way relapses are being first identified as an ocular presentation. All hematological malignancies may involve many ocular tissues either by direct infiltration, hemorrhage, ischemia, or toxicity due to various chemotherapeutic agents. Ocular involvement may also be seen in graft-versus-host reaction in patients undergoing allogeneic bone marrow transplantation, or simply as increased susceptibility to infections as a result of immunosuppression that these patients had undergone. This can range from simple bacterial conjunctivitis to an endophthalmitis. These malignancies can present as pathology in the adnexae, conjunctiva, sclera, cornea, anterior chamber, iris, lens, vitreous, retina, choroid, and optic nerve. Recognition of the varied ocular presentations is also important in assessing the course and prognosis of the disease (23).

Osama Badeeb et al reported that Leukemia may affect any ocular tissue at some time during its course. The incidence of ocular involvement may be as high as 90%. Elise Torczynski et al. had reported primary ophthalmic leukemia infiltrate in 3% and secondary ophthalmic

findings in 39% and ocular changes unrelated to leukemia in 20% of their patients. Acute leukemias affect the eye four times as frequently as the chronic types (9).

The retina is the most common ocular tissue to be involved in leukemia; Duke-Elder suggests that up to 90% of patients will develop retinopathy at some stage of their disease

On histopathological examination, the choroid is the most common ocular tissue to be involved in leukemia (85%) but this is rarely visible clinically.

The optic nerve is affected in 34% of the cases and the iris and anterior segments are affected in 0.5% to 2.6. This study showed that 17 (54.8%) of the 31 leukemia patients had ocular abnormalities related to leukemia

In a study by Schachat et al, it was reported that Leukemic infiltrates were present in 3% of patients, other findings related to leukemia were seen in 39% of patients, and 20% of patients had unrelated abnormalities. Visual loss was seen in at least 5% of the patients (24)

AGE INCIDENCE:

In this study out of 50 patients, 6 were in the age group of 0-9 years (12%); 8 patients were in the age group of 10-19 yrs(16%); 9 patients were in the age group of 20-29yrs(18%); 10 each were in the age

group of 30-39 yrs and 40-49 yrs (20%); 4 patients in the age group of 50-59 yrs(8%); 2 patients in the age group of 60-69 yrs(4%) and 1 patient in the age group of 70-79 yrs(2%);

In this study the ocular features were present in the age group between 2 to 72 yrs. The youngest person was 2 yrs old. Moll et al in a Polish article studied children in the age group between 0.5 -17 yrs revealing ocular manifestations in 54% of their study group (8).

In this study the ocular features involved both the anterior segment and the posterior segment of the eye. Predominantly anterior segment findings were found only in 1 case of each age group with a maximum of 2 in the age group between 20-29 yrs and 40-49 yrs. The posterior segment findings were predominant in all the age groups with a maximum of 5 in the age group between 0-9 yrs. Only those patients in the age group between 50-59 yrs had no patients with either anterior or posterior segment findings.

Osama Badeeb et al reported a study in which patients with leukemia ranged from 0.8 to 70 years with a median of 12.5 years. The interval between the diagnosis of leukemia and the first ocular manifestation was ≤six months in 11 patients and 24 to 60 months in six patients. In this study the lowest interval between the diagnosis of malignancy and the first ocular manifestation was 1 month reported in 3 patients(9).

Eight patients with mean age of 61.25 years (range 42-78) who exhibited ophthalmic manifestations of multiple myeloma were studied by Shirley Fung et al, in which they found that 50% of their patients had neuro-ophthalmic symptoms and 37.5% presented with orbital involvement.

In a study by Reddy et al they reported that the eye changes were seen more often in adults (49.1%) than in children (16.5%). In this study also the ocular manifestations were more common in adults (59.09%) than in children (40.91%) (25).

SEX INCIDENCE:

In this study out of the 50 patients 32 were males (64%) and 18 were females (36%). Of the 32 males, in the 16patients who had ocular features, around 12 patients had predominantly posterior segment findings. 2 patients had anterior segment features and 3 with neurologic findings. Of the 18 females, in the 7 patients who had ocular features, a maximum of 4 patients presented with posterior segment features and 1 patient had anterior segment feature. 2 patients had neurological findings. In this study, ocular manifestations were more common in males (50%) than in the females (38.9%). And in both the sex groups, the posterior

segment features were predominating. This difference follows the higher incidence of haematological malignancies in males.

INCIDENCE OF OCULAR FEATURES AMONG VARIOUS DISEASES:

Out of the 50 patients in the study group 7 patients had Non-Hodgkins lymphoma with 2 patients with ocular features (28.6%). Hodgkins disease was present in 9 patients with only 2 patient having ocular manifestation (22.2%). 5 out of the 11 patients with multiple myeloma had ocular features (45.5%). Chronic myeloid leukemia was present in 4 patients, out of which 3 patients had ocular features (75%). Chronic lymphoid leukemia was present in 4 patients with only 1 patient having ocular signs (25%). Acute lymphatic leukemia was present in 9 patients with 6 patients having ocular signs (66.6%) and acute myeloid leukemia in 6 patients with 4 patients having ocular manifestations (66.6%).

Moll et al in a study of 39 children (age 0.5-17 years) with leukemia or lymphoma, reported that ocular manifestations were present in 54% of study group (21 children) (8)

Shirley Fung et al in a study of 8 patient, six patients (75%) had known MM at the time of their ophthalmic evaluation, reported that

ophthalmic manifestations of MM are uncommon and diverse. They may appear at the initial presentation of the disease or occur late in the disease process (21).

Osama badeeb et al studied 31 leukemic patients of which 17 (54.8%) patients had ocular abnormalities related to leukemia. Most ocular changes occurred in the acute forms of leukemia as previously reported. This is because the acute forms of leukemia are the most common and involve the CNS more frequently than do the chronic forms (9). Which is comparable to the present study which also shows more incidence of ocular features in acute (66.6%) than in chronic malignancies(50%).

Schachat et al in their study had reported primary ophthalmic leukemia infiltrate in 3% and secondary ophthalmic findings in 39% and ocular changes unrelated to leukemia in 20% of their patients (24).

DIFFERENT TYPES OF OCULAR MANIFESTATIONS:

The various ocular manifestations of hematological malignancies can be broadly divided into anterior segment and posterior segment findings. In this study, among all the diseases the posterior segment findings were predominating including the retinal and pre-retinal hemorrhages, vitreous hemorrhage, Roth spots, sub-retinal hemorrhages,

papilledema, retinal detachment and posterior uveitis, constituting about 72% of the ocular manifestations.

The anterior segment findings were dry eye, sclerokeratitis, anterior uveitis constituting 12% pf the ocular manifestations; and neurological manifestations were nerve palsies and proptosis, forming 5 cases of the total about 16%.

Moll A et al in their study found that the most frequent ocular findings were seen in conjunctiva (33.4%). 15.4% patients presented with posterior segment findings, without loss of ocular acuity. Other manifestations were dry eye syndrome and proptosis(8).

Osama badeeb et al in their study found that ocular manifestations could be related to direct infiltration of the eye by leukemic cells, or secondary to anemia, hyperviscosity, increased intracranial pressure, pancyto-penia and treatment with irradiation or chemotherapy. Primary leukemic infiltrate was observed in 14 (45.2%) of the ocular relapses in the form of Anterior segment leukemic infiltrate(ASLI), optic nerve and ciliary body infiltrate, glaucoma, proptosis, choroidal and retinal detachment. Most ocular changes occurred in the acute forms of leukemia. This is because the acute forms of leukemia are the most common and involve the CNS more frequently than do the chronic forms (9). In contrary to this study they observed that the anterior segment of the eye was commonly involved in their study.

They also found that the optic nerve was involved in nine of the leukemic relapses, most often while the patients were in CNS relapse. Leukemic infiltrate of the optic nerve, in contrast to papilledema, is often unilateral. When it occurs bilaterally, however, it may be difficult to differentiate clinically from papilledema. . In papilledema secondary to increased intracranial pressure due to CNS leukemic infiltration, there was dilatation of the brain ventricles, swollen sheath, tortuous optic nerves and engorged orbital vessels. Orbital CT scan was found to be useful in confirming retrobulbar optic nerve infiltrate. The conjunctival involvement was secondary to thrombocytopenia. Cranial nerve palsy secondary to CNS infiltrate in 3 patients. Two of their patients who had ALL developed proptosis(9). In the present study there is one case of papilledma, but no case of optic nerve infiltration.

Cysts of the ciliary body and retinal vascular lesions represent the most common ocular manifestations in myeloma patients. Paris et al reported a case of anterior chamber infiltration–simulating hypopyon (pseudohypopyon) in multiple myeloma(10). Matano et al reported a patient with AML who developed leukemic hypopyon(33). David et al reported a treatment-resistant unilateral hypopyon in the remission phase of ALL(42).

Saenz frances et al reported a case of bilateral papilledema secondary to chronic lymphocytic leukemia. In this study there was just

one patient with bilateral established papilledema in a case of acute myeloid leukemia (11).

In this study there was a case of anterior uvieits that occurred in a case of acute lymphoblastic leukemia. Similiarly Elise Torczynski et al reported a case of anterior uveitis occurring in acute lymphoblastic leukemia (27). Atchaneeyasakul et al reported a case of relapsing ALL ahich presented as anterior uveitis (34). Molina Garrido et al reported a B-cell lymphochytic lymphoma, which presented as bilateral posterior uveitis (35).

Francois Thoumazet et al reported 2 cases of multiple myeloma presenting with orbit and muscle involvement and distal bony erosion (20). Shimada et al reported a case of bilateral optic neuropathy associated with multiple myeloma(13).

Rosenthal AR reported that retinal microaneurysms, capillary closure, and neovascularization have been documented in individuals with chronic leukemia. Optic nerve, choroid and iris infiltration can also occur (28).

In this study there were 11 patients with multiplemyeloma of which 5 had varying ocular features like sclerokeratitis, vitritis, pre-retinal hemorrhages, vitreous haemorrhage and 6th nerve palsy. Shirley fung reported that in a study among 8 patients of multiple myeloma, four patients (50%) had neuro-ophthalmic manifestations resulting in diplopia

or visual disturbances. Three patients (37.5%) presented with orbital involvement and 1 (12.5%) with hyperviscosity retinopathy. Five patients (62.5%) died within 2 months of their ophthalmic presentation. And those ophthalmic manifestations of Multiple Myeloma are uncommon and diverse. They may appear at the initial presentation of the disease or occur late in the disease process (21). Shakin EP et al reported a case of infiltration of the iris that simulated a nongranulomatous uveitis (39). Kazuhiro Yamada et al reported a case of primary B-cell non-Hodgkins lymphoma with anterior uveitis resulting from primary malignant lymphoma in the iris (41)

Pradhan S et al reported a case of Multiple myeloma with bilateral tearing secondary to infiltrative lesions of the lacrimal sacs (40).

Fackler et al reported a case of acute lymphoblastic leukemia presenting as bilateral serous macular detachments (16).

In this study there was a patient with ALL who presented with unilateral rhegmatogenous retinal detachment. B. A. Michael.S.Peterson et al report unusual retinal manifestation of intraocular lymphoma secondary to systemic non-Hodgkins' lymphoma. Ocular inflammation is common with these tumors and presents a diagnostic challenge to clinicians who discover assumed idiopathic uveitis in older patients which is refractory to steroid treatment (29).

T-cell lymphomas are a type of non-hodgkin's lymphoma in which ophthalmic manifestations are very rare. Only a total of 20 cases have been reported and about half in association with mycoses fungoides. A case with intra-ocular metastases to the Iris and ciliary body which presented as granulomatous iritis was reported by Ove.A.Jensen et al (30).

Glavici.M reported a case of iridic nodular lesion which had appeared in the evolution of a non-Hodgkin malignant lymphoma in a 8-year old boy (31). Non-Hodgkin's lymphomas can simulate uveitis (32). Werschnik C et al described a patient with tumor of the optic disk in one eye and bilateral uveitis with secondary glaucoma (36).

Neuro-ophthalmological complications of lymphoma are numerous and occur mostly in the setting of a known lymphoma or as the sign of a recurrence. Henchoz L et al has described a case of simultaneous bilateral optic neuropathy as the initial clinical manifestation of a non-Hodgkin malignant lymphoma (37). There is also a report of a bilateral uveitis and marked bilateral nonrhegmatogenous retinal detachment near the optic disk occurring in a case of B-cell derived type of non-hodgkins lymphoma reported by Kormann BA et al(38).

CORRELATION OF VISUAL ACUITY AT THE TIME OF PRESENTATION:

In this study almost 42% of the patients who presented to us with hematological malignancies had a vision of around 6/6 – 6/9. 22% of the patients had 6/12 – 6/18 vision. About 21% of them had 6/24 – 6/36. 15% of the patients had a vision of 6/60 or worse. In this study the poor vision is attributed to pre-retinal haemorrhage at the macula, vitritis, axial proptosis, vitreous haemorrhage, retinal detachment, cavernous sinus infiltration and sixth nerve palsy.

Hendrik AM et al found that a number of ocular problems compromising vision occurred in a patient with chronic myeloid leukemia following blastic transformation. Hemorrhagic retinopathy developed with systemic relapse and resolved with control of systemic disease. Optic nerve involvement occurred with meningeal leukemia. bilateral vitreous hemorrhages occurred, severely impairing vision. Leukemic infiltration of the eye may occur with increasing frequency in CML as the survival following bastic transformation improves. Infiltration should be recognized and treated promptly if serious loss of vision is to be avoided (26).

CONCLUSION

- Ophthalmic manifestations of haematologic malignancies are more common in the age group between 0-9 yrs (100%); Next common age group is 20-29 yrs (55%).
- The posterior segment findings were predominant in all the age groups with a maximum of 5 in the age group between 0-9 yrs.
- The ocular features in cases of haematologic malignancies are more common in the males (64%)
- Eye findings were more prevalent in the leukemia's than in lymphomas and multiple myeloma.
- Eye findings were more commonly seen in acute than in chronic malignancies
- Amongst the individual diseases, chronic myeloid leukemia had a maximum incidence of ophthalmic manifestations (75%).
- Among the different types of manifestations, the posterior segment manifestations were predominating in most of the age groups and in most of the individual disease entities.

- Among the various types of posterior segment manifestations, retinal haemorrhage, pre-retinal haemorrhage and roth spots predominated. The neurological involvement in the form nerve palsies also contributed significantly.
- Regarding the visual acuity at the time of presentation of the ocular features, most of the patients had a good acuity of 6/6-6/9 in 43%.

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PROFORMA

NAME

AGE

SEX

IP/OP NO:

ADRESS:

C/O Defective vision/ blurred vision

Duration

Loss of vision

Headache/ Polyuria/ Haematuria

Vomitting/Haematemesis/Haemoptysis

Floaters

Giddiness/Chest pain/ Palpitation

Fever

Photophobia

Treatment History: Duration of malignancy

H/O Drug intake- yes/no- specify

Duration

Regular/irregular

Symptomatic relief- adequate/ not adequate

H/o discontinuation of drugs

Past History:

Initial symptoms that lead to the diagnosis of the disease

H/O Hypertension/Diabetes/ Stroke/ Myocardial infarction/Peptic ulcer/

Ischemic heart disease

Family History:

H/O similar illness in the other family members

EXAMINATION

GENERAL EXAMINATION

General Condition- good/fair/poor

CVS-

RS-

CNS-

Abdomen-

Pulse rate-

Blood Pressure-

Cyanosis/ Pallor/ Icterus/ Clubbing/ Pedal edema

OPHTHALMIC EXAMINATION:

Facial Asymmetry- yes/no

Head posture-Normal/Abnormal

Local Examination:

Left Eye		Right Eye
	Lids	
	Conjunctiva	
	Cornea	
	Anterior chamber	
	Iris	
	Pupil	
	Lens	
	EOM	

Vision

Tension

Gonioscopy

Fundus:

Direct Ophthalmoscopy

Indirect Ophthalmoscopy

INVESTIGATIONS

Haemoglobin

Blood sugar

Urea

Creatinine

Blood smear

Total count

Differential count

Erythrocyte sedimentation rate

X-Ray Chest PA view

ECG in all leads

Bone marrow smear

Fundus flurescein angiography

USG B-Scan

CML Chronic Myeloid Leukemia

CLL Chronic Lymphoid Leukemia

MM Multiple Myeloma

CFCF Counting Fingers Close to Face

HM Hand Movements

PL Perception of Light